PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 July 2001 (11.07.01)	
International application No. PCT/CA00/01139	**Applicant's or agent's file reference** 10024-3/JHW
International filing date (day/month/year) 29 September 2000 (29.09.00)	**Priority date** (day/month/year) 30 September 1999 (30.09.99)
Applicant THOMPSON, Michael et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 April 2001 (02.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was [ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Charlotte ENGER Telephone No.: (41-22) 338.83.38

WO 01/23892
PCT/CA00/01139

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:
WOODLEY, John, H.
Sim & McBurney
6th Floor
330 University Avenue
Toronto, Ontario M5G 1R7
CANADA

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year)
05 April 2001 (05.04.01)

Applicant's or agent's file reference
10024-3/JHW

IMPORTANT NOTICE

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/CA00/01139	29 September 2000 (29.09.00)	30 September 1999 (30.09.99)

Applicant
SENSORCHEM INTERNATIONAL CORPORATION et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
05 April 2001 (05.04.01) under No. WO 01/23892

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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Authorized officer
J. Zahra

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
10024-3/JHW		
International application No. PCT/CA 00/01139	International filing date (*day/month/year*) 29/09/2000	(Earliest) Priority Date (*day/month/year*) 30/09/1999
Applicant SENSORCHEM INTERNATIONAL CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ______

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[illegible] 00/01139

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/543 C12Q1/68 G01N27/00 G01N29/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, INSPEC, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 374 521 A (KIPLING ARLIN L ET AL) 20 December 1994 (1994-12-20) cited in the application column 1, line 66 -column 2, line 3 column 2, line 40 - line 46 column 3, line 23 - line 45 column 5, line 10 - line 21 column 5, line 43 - line 46 column 5, line 59 - line 66 ---	1-13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2001	19/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Joyce, D

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INTERNATIONAL SEARCH REPORT

International Application No
PCT[illegible]00/01139

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	FERRANTE F ET AL: "MOLECULAR SLIP AT THE SOLID-LIQUID INTERFACE OF AN ACOUSTIC-WAVE SENSOR" JOURNAL OF APPLIED PHYSICS,US,AMERICAN INSTITUTE OF PHYSICS. NEW YORK, vol. 76, no. 6, 15 September 1994 (1994-09-15), pages 3448-3462, XP000470063 ISSN: 0021-8979 cited in the application column 6, line 12 - line 14 column 16, paragraph 1 ---	1-13
A	US 5 306 644 A (MYERHOLTZ CARL A ET AL) 26 April 1994 (1994-04-26) column 5, line 22 - line 43 ---	4-10
A	US 4 735 906 A (BASTIAANS GLENN J ET AL) 5 April 1988 (1988-04-05) abstract column 8, line 63 - line 65 ---	1,2,5,6
A	US 5 658 732 A (EBERSOLE RICHARD CALVIN ET AL) 19 August 1997 (1997-08-19) cited in the application column 5, line 2 - line 18 column 6, line 24 - line 37 ---	1,5,6
A	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 10, 31 August 1998 (1998-08-31) & JP 10 115648 A (ADVANTEST CORP), 6 May 1998 (1998-05-06) abstract -----	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/[illegible]00/01139

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
US 5374521	A	20-12-1994	CA	2078184	A,C	18-03-1993
US 5306644	A	26-04-1994	US	5130257	A	14-07-1992
			US	5283037	A	01-02-1994
			DE	4409588	A	06-10-1994
			JP	6308127	A	04-11-1994
			EP	0361729	A	04-04-1990
			JP	2122242	A	09-05-1990
			DE	69027077	D	27-06-1996
			DE	69027077	T	02-10-1996
			EP	0416730	A	13-03-1991
			JP	3100438	A	25-04-1991
			EP	0542469	A	19-05-1993
			JP	5240762	A	17-09-1993
US 4735906	A	05-04-1988	NONE			
US 5658732	A	19-08-1997	CA	2066643	A	05-04-1991
			DE	69010506	D	11-08-1994
			DE	69010506	T	22-12-1994
			EP	0494896	A	22-07-1992
			JP	5500715	T	12-02-1993
			WO	9105261	A	18-04-1991
JP 10115648	A	06-05-1998	NONE			

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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(25) Filing Language: English

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(30) Priority Data:
60/156,714 30 September 1999 (30.09.1999) US

(71) Applicant *(for all designated States except US)*: SENSORCHEM INTERNATIONAL CORPORATION [CA/CA]; 170 College Street, Room 308A, Toronto, Ontario M5S 3E3 (CA).

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(74) Agent: WOODLEY, John, H.; Sim & McBurney, 6th Floor, 330 University Avenue, Toronto, Ontario M5G 1R7 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/23892 A1

(54) Title: TRAVERSE SHEAR MODE PIEZOELECTRIC CHEMICAL SENSOR

(57) Abstract: The present invention relates to a process for sensing biological or chemical changes in molecular structural shape or mass of molecules attached to the surface of a transverse shear piezoelectric oscillating molecular sensing device driven by a network analyzer. The process comprises the steps of i) exciting the sensor device at a series of predetermined frequencies, ii) collecting data to determine values for the predetermined parameters of series resonance frequency shift (fS), motional resistance (RM), motional inductance (LM), motional capacitance (CM), electrostatic capacitance (Co) and boundary layer slip parameter (α); and iii) determining relative changes in the measured parameters to detect thereby any changes in molecular structural shape or mass at sensing device surface.

TRAVERSE SHEAR MODE PIEZOELECTRIC CHEMICAL SENSOR

Field of the Invention

This invention relates to a process of detecting specific molecules in a liquid (the analyte) with receiving molecules, (the receptors) which are attached to the surface of a thickness shear mode acoustic sensor (TSM). Acoustic energy generated in the sensor is transferred to and from the fluid depending on the surface coupling behaviour. The coupling is altered when the analyte binds to the receptor producing easily measured changes in the electrical characteristics of the sensor.

The invention further relates to the application of the measurement of the coupling effects to the sensing of biomolecules, and other molecules of biological significance such as drugs, in general. For example, the receptor may be a protein, a single oligonucleotide strand, DNA or RNA and the analyte a protein, drug or complementary strands of DNA or RNA. The interaction between the analyte and the sensor bound receptor can be identified through a quantitative TSM response. Other measurement scenarios are possible through the detection of changes in the acoustic coupling between the sensor surface and the surrounding liquid.

Background of the Invention

A TSM sensor is a device which generates mechanical vibrations from an electrical signal and uses these vibrations to detect and/or quantify particular chemical or biochemical substances present in a medium surrounding the sensor (the analyte). Acoustic energy is stored and dissipated both in the device itself, and through interfacial coupling, in a surrounding liquid medium. By coating the sensor with one or more layers of a substance which interacts with the analyte, the energy storage and transfer processes change when the interaction occurs. This changes the acoustic resonance of the sensor, which can be observed by measuring the electrical impedance of the sensor. The

applicants have published several papers in this field and they are listed as follows:

1) F. Ferrante, A.L. Kipling and M.Thompson, "Molecular Slip At The Solid-Liquid Interface Of An Acoustic Wave Sensor", *J. Appl. Phys.* 76(6):3448-3462, 1994;

2) G.L. Hayward and M. Thompson, "A Transverse Shear Model Of A Piezoelectric Chemical Sensor", *Amer. Inst. Physics* 83(40:2194-2201, 1998;

3) Cavic B.A. et al., "Acoustic Waves And The Real-Time Study Of Biochemical Macromolecules At The Liquid/Solid Interface", *Faraday Discuss.* 107:159-176, 1997;

4) H. Su and M. Thompson, "Rheological And Interfacial Properties Of Nucleic Acid Films Studies By Thickness-Shear Mode Sensor And Network Analysis", *Can. J. Chem.* 74:344-358, 1996.

There are several mechanisms whereby a TSM sensor responds to chemical change on its surface when it is immersed in a liquid. Surface mass deposition occurs when the analyte binds to the receptor on the sensor surface. This increases the storage of acoustic energy through the inertia of the added mass. Acoustic energy may also be stored through the elastic deformation of a coating on the surface. The elasticity of the coating may also change when the analyte binds to the receptor coating. These energy storage modes determine the resonant characteristics of the sensor which can easily be measured electrically. These processes are well known. Examples of piezoelectric sensors are described, for example in U.S. Patents 5,374,521 and 5,658,732.

Viscous loading occurs when acoustic energy is transferred to the liquid. Some of the acoustic energy is stored by the inertia of the fluid moving with the sensor surface and can be transferred back to the sensor, but acoustic energy is also dissipated by internal friction within the fluid. The viscous loading effect is also well known, however in the current use of this effect, the transfer of acoustic energy at the surface is considered to be perfect, that is, there is no slip between the sensor surface and the adjacent fluid molecules.

The current practice is based on the well known Butterworth - van Dyke model of a piezoelectric resonator which consists of a resistor, inductor and capacitor in series, all in parallel with another capacitor. The series arm of this network is called the motional arm. Further details of this model and the calculation of the following parameters may be found in the above paper entitled "Rheological and Interfacial Properties of Nucleic Acid Films Studies by Thickness-Shear Mode Sensor and Network Analysis".

Motional Inductance

The motional inductance, L_M, represents the inertial energy stored by the sensor. It depends on the mass of the TSM sensor as well as the mass of material (the analyte) added to the surface. Since liquid coupled to the surface can store and return acoustic energy, L_M is also dependent on the viscosity of the liquid.

Motional Resistance

The motional resistance, R_M, is intrinsically related to the energy dissipated by the sensor.

Accordingly, any imposition of material (or loss of material) that has a viscous property or changes in the viscosity of the liquid will result in a change in the energy dissipation and hence R_M.

Motional Capacitance

The motional capacitance, C_M, represents the elastic energy stored by the sensor. The absorption or chemical binding of the analyte to the coating can have a large effect on the viscoelastic properties of the coating. Depending on the thickness, an added (or removed) layer of material may change the elasticity of the sensor and thus affect C_M. Although most fluids are considered to be viscous, at the high frequencies used in piezoelectric quartz sensors, the liquid may also have elastic properties.

Static Capacitance

The static capacitance C_O represents the dielectric constant of the quartz, but includes that of the medium through the electric field. Charge interactions between the analyte and the sensor coating will affect this value.

Summary of the Invention

According to an aspect of the invention, there is provided a process for sensing biological or chemical changes in molecular structural shape or mass of molecules attached to the surface of a transverse shear piezoelectric oscillating molecular sensing device driven by a network analyzer, said process comprising:

i) exciting said sensor device at a series of predetermined frequencies;

ii) collecting data to determine values for the predetermined parameters of series resonance frequency shift (fS), motional resistance (RM), motional inductance (LM), motional capacitance (CM), electrostatic capacitance (Co) and boundary layer slip parameter (α); and

iii) determining relative changes in said measured parameters to detect thereby any changes in molecular structural shape or mass at sensing device surface.

In accordance with another aspect of the invention there is provided a method of determining the efficiency of acoustic coupling between a sensor and the surrounding fluid, said method comprising:

a) applying an electrical signal of known frequency and voltage to the sensor;

b) measuring the current through the sensor to determine the impedance at the known frequency;

c) repeating steps a) and b) over a range of frequencies to generate a set of impedance data; and

d) fitting the measured impedance data to determine an α parameter which represents coupling strength.

Detailed Description of the Preferred Embodiments

This invention is based on the measurement of phenomena based on imperfect acoustic coupling between the sensor surface and the liquid. The nature of this coupling determines the strength of the viscous loading and elastic effects depending on such parameters as the surface free energy and the molecular conformation of the sensor coating. These molecular parameters are very sensitive to chemical changes at the surface and therefore acoustic coupling provides a novel sensing mechanism.

The impedance measurements are carried out by applying an electrical signal of known frequency and voltage to the sensor and measuring the current through the sensor. Through Ohm's law, this provides the impedance at the known frequency. By performing this measurement over a range of frequencies, a set of data is generated. The above described, specifically selected parameters of L_M, R_M, C_M and C_O have been found to be the determining parameters for indicating a mass or conformation change at the TSM surface. Hence these parameters are fitted to the data.

While the Butterworth - van Dyke model provides useful information, it is an electrical analogy which presents the information unclearly. An alternate model of the TSM sensor is based on a solution of the equations of motion and electric fields. With this second model as set out in the aforementioned paper entitled "Molecular Slip At The Solid-Liquid Interface Of An Acoustic Wave Sensor" and "A Transverse Shear Model Of A Piezoelectric Chemical Sensor", the deposited mass and the coupling may be determined directly by fitting the

electrical impedance data obtained as above. The coupling is represented by a slip parameter, α, which arises from a slip boundary condition used in solving the set of equations. The common approach is to assume perfect coupling and to set $\alpha = 1$. In this invention, α is taken to be a complex number which is determined by fitting the measured impedance data.

The sensing process is understood to be occurring at the interface between the solid device and the liquid medium. Ligands for biological macromolecules include small molecules, ions, proteins, peptides, and strands of both DNA and RNA. The interaction of these entities with the biological molecules attached to the sensor will cause an alteration of the physical properties of the film resulting, in turn, in changes in the measured parameters. These changes will very clearly result from a combination of some or all of the above response mechanisms particular for each chemical situation. In this regard, the dimensions of the newly bound ligand is an important consideration.

The signaling species coated onto the acoustic biosensor are proteins (antibodies, enzymes, hormones, molecular receptors, etc.) and nucleic acids oligonucleotides, DNA and RNA) attached to the device surface. These molecules exist in a highly hydrated form which can be considered to constitute very viscous gels.

The effect of viscous loading is the result of acoustic energy transfer to and from the surrounding medium. This in turn depends on the nature of the contact between the surface and the medium. The contact is controlled by such chemical properties as hydrogen bonding, dispersion interactions and interfacial charge. The process can be viewed as a drag existing between the surface coating and the liquid. α represents the coupling strength but also contains phase shift information. This provides additional information regarding relative mass of liquid molecules compared to those of the sensor surface and when correlated with the selected Butterworth – van Dyke model provide a determination on what is happening at the TSM surface, namely, mass and/or molecular structural shift or change in conformation.

Example

The human immunodeficiency virus type I (HIV-I) is strongly regulated at the transcriptional level by the interaction of an 86-amino acid protein, Tat, with the trans activation responsive element at the 5' -end of the viral messenger RNA transcript (TAR). The TAR-Tat system is an important target for drug discovery research because the binding of the regulatory protein to TAR can be blocked by small molecules.

In this application we compute the slip parameter α , for the binding of Tat-derived peptides to TAR immobilized on a sensor surface. The TAR RNA is synthesized, with a biotin moiety at the 5' -end, on a DNA synthesizer by standard phosphoramidite chemistry. The acoustic wave sensor is incorporated into a flow-through configuration and electrically connected to an acoustic network analyzer. A dispersion of 100-500 μl of the reagent neutravidin is injected into the apparatus and the protein adsorbs to the gold electrode surface of the acoustic wave sensor. A dispersion of biotinylated TAR- RNA (100-500 μl) is introduced into the system where the formation of the biotin-avidin complex results in attachment of TAR to the sensor surface. Various Tat-derived peptides are then introduced into the flow-trough system. In this particular application the following peptides are specified: tat_{12}, tat_{20}, and tat_{30} where the subscript refers to the number of amino acids in the peptide. Dispersions of peptide (100-500 μl) are injected into the system. On binding of peptide to TAR in real time transient responses in the aforementioned parameters are obtained. The computed $\propto$ parameter for the various responses, which distinguishes the nature on binding, are as follows:

Tat_{12} baseline 1.978 @20.85 degrees
signal 1.964 @ 20.97 degrees

Tat_{20} baseline 1.985 @21.42 degrees
signal 1.926@ 18.15 degrees

Tat_{30} baseline 1.982 @ 22.61 degrees

signal 1.994 @ 23.03 degrees

Tat_{12} displays a small decrease in slip magnitude with an increase in phase, whereas tat_{20} shows large decreases in magnitude and phase. Tat_{30} depicts smaller increase in magnitude and phase.

Although preferred embodiments of the invention have been described herein in detail, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention or the scope of the appended claims.

CLAIMS:

1. A process for sensing biological or chemical changes in molecular structural shape or mass of molecules attached to the surface of a transverse shear piezoelectric oscillating molecular sensing device driven by a network analyzer, said process comprising:

i) exciting said sensor device at a series of predetermined frequencies ;

ii) collecting data to determine values for the predetermined parameters of series resonance frequency shift (fS), motional resistance (RM), motional inductance (LM), motional capacitance (CM), electrostatic capacitance (Co) and boundary layer slip parameter (α); and

iii) determining relative changes in said measured parameters to detect thereby any changes in molecular structural shape or mass at sensing device surface.

2. The process according to claim 1 further comprising the step of:

iv) correlating said changes with a calibrated set of data for said parameters to determine a value for change in molecular conformation and/or molecular mass.

3. The process according to claim 1 wherein a change in slip parameter (α) and an essentially zero change in series resonant frequency shift confirms a change in molecular structural shape and essentially zero change in mass.

4. The process according to claim 1 wherein said changes in molecular mass or conformation are generated by an interaction between entities bound to the sensor and molecules in the surrounding liquid medium.

5. The process according to claim 4 wherein said entities bound to the sensor are selected from the group consisting of proteins and nucleic acids.

6. The process according to claim 5 wherein said proteins are selected from the group consisting of antibodies, enzymes, molecular receptors, receptor ligands and polypeptides.

7. The process according to claim 5 wherein said nucleic acids are selected from the group consisting of DNA, RNA and oligonucleotides.

8. The process according to claim 4 wherein said molecules in liquid medium are selected from the group consisting of proteins and nucleic acids.

9. The process according to claim 8 wherein said proteins are selected from the group consisting of antibodies, enzymes, molecular receptors, receptor ligands and polypeptides.

10. The process according to claim 8 wherein said nucleic acids are selected from the group consisting of DNA, RNA and oligonucleotides.

11. A method of determining the efficiency of acoustic coupling between a sensor and the surrounding fluid, said method comprising:

a) applying an electrical signal of known frequency and voltage to the sensor;

b) measuring the current through the sensor to determine the impedance at the known frequency;

c) repeating steps a) and b) over a range of frequencies to generate a set of impedance data; and

d) fitting the measured impedance data to determine an α parameter which represents coupling strength.

12. The method according to claim 11, wherein the α parameter is other than 1.

13. The method according to claim 11 wherein the magnitude of said α parameter is dependant on molecular mass and/or molecular conformation at the sensor surface.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/01139

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/543 C12Q1/68 G01N27/00 G01N29/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, INSPEC, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 374 521 A (KIPLING ARLIN L ET AL) 20 December 1994 (1994-12-20) cited in the application column 1, line 66 -column 2, line 3 column 2, line 40 - line 46 column 3, line 23 - line 45 column 5, line 10 - line 21 column 5, line 43 - line 46 column 5, line 59 - line 66 ---	1-13

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2001	19/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Joyce, D

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/01139

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FERRANTE F ET AL: "MOLECULAR SLIP AT THE SOLID-LIQUID INTERFACE OF AN ACOUSTIC-WAVE SENSOR" JOURNAL OF APPLIED PHYSICS, US, AMERICAN INSTITUTE OF PHYSICS. NEW YORK, vol. 76, no. 6, 15 September 1994 (1994-09-15), pages 3448-3462, XP000470063 ISSN: 0021-8979 cited in the application column 6, line 12 - line 14 column 16, paragraph 1	1-13
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